REMARKS

Claims 2, 3, 6-9, 12-15, 17-34, 36, and 50 are pending and at issue.

Applicant requests clarification concerning the remarks on page 2 of the Office Action stating that "Applicants' argument, filed on 24 July 2007, has been fully considered and it is deemed to be persuasive regarding [the] previous rejection[s]." Applicant notes that the most recent previous amendment was filed on August 1, 2008 and that all previous rejections have been maintained by the Examiner.

First Rejection under 35 U.S.C. §103(a) – Obviousness

Claims 2, 3, 6-9, 12, 17-20, 26, 27, 32, 36, and 50 remain rejected as obvious over U.S. Patent No. 6,194,420 ("Lang") in view of U.S. Patent No. 6,221,383 ("Miranda") and in further view of U.S. Patent No. 6,024,975 ("D'Angelo"). The Examiner asserts that Lang teaches anagrelide containing pharmaceutical compositions to treat essential thrombocythemia. According to the Examiner, Miranda describes the transdermal administration of anagrelide. The Examiner asserts that D'Angelo teaches the transdermal delivery of drugs using a patch system. The Examiner contends that one of ordinary skill in the art would be motivated to combine the teachings of Lang with the teachings of Miranda because both describe the administration of anagrelide as part of a pharmaceutical composition. The Examiner further asserts that one skilled in the art would combine the teachings of Lang, Miranda, and D'Angelo because when the teachings of Lang and Miranda are combined, these teachings overlap with D'Angelo in subject matter, *i.e.*, the administration of medicaments, particularly anagrelide, by transdermal delivery.

Second Rejection under 35 U.S.C. §103(a) – Obviousness

Claims 21-23 and 28 and 30 remain rejected as obvious over Lang in view of D'Angelo and further in view of U.S. Patent No. 5,133,972 ("Ferrini"). The Examiner incorporates by reference the discussion of Lang and D'Angelo from the above rejections. Ferrini, according to the Examiner, teaches a multilayered therapeutic system for the transdermal administration of an active

ingredient. The Examiner asserts that a skilled artisan would be motivated to combine Lang, D'Angelo, and Ferrini because each describes the administration of medicaments by transdermal delivery.

Third Rejection under 35 U.S.C. §103(a) – Obviousness

Claims 24-25, 29, 31, 33-34, and 36 have been rejected as obvious over Lang in view of D'Angelo and in further view of U.S. Patent No. 4,847,276 ("Yarrington"). The Examiner incorporates by reference the discussion of Lang and D'Angelo from the above rejections. The Examiner asserts that Yarrington teaches the treatment of thrombocythemia by the administration of anagrelide using particular regimens. According to the Examiner, one of ordinary skill in the art would be motivated to combine the teachings of Lang, D'Angelo, and Yarrington because each relate to the treatment of thrombocythemia.

For all three of these obviousness rejections, the examiner contends in an Office Action mailed April 16, 2008 that "Applicant has elucidated an inherent biochemical mechanism regarding the administration of anagrelide." *See*, *e.g.*, page 3 of the Office Action.

Response to Obviousness Rejections

The claimed invention would not have been predictable and, therefore, would not have been obvious.

As explained by MPEP §2121(I),

> When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007).

In the present application, the Examiner has cited Lang, Miranda, D'Angelo, Ferrini, and Yarrington in the obviousness rejections. Lang and Yarrington teach the use of anagrelide to treat thrombocythemia. Miranda discloses the transdermal use of anagrelide, as one drug in a list of over

a dozen, to treat thrombosis. D'Angelo describes a transdermal drug delivery system. Ferrini describes the transdermal administration of methanediphosphonic acid derivatives. Based on Applicant's understanding of the obviousness rejections, the Examiner argues that it would have been obvious to one of ordinary skill in the art to replace the treatment of thrombosis as taught by Miranda with the treatment of thrombocythemia as disclosed in Lang and Yarrington to yield the claimed invention since anagrelide treats thrombosis by reducing the number of blood platelets, thrombocythemia is a condition in which a patient has an excess of platelets, thus, it would have been expected that transdermally administered anagrelide could treat thrombocythemia by lowering the number of blood platelets.

While it may be the case that anagrelide treats thrombosis by reducing the number of blood platelets and thrombocythemia is a condition in which a patient has an excess of platelets, it is not the case that the claimed invention of transdermally administered anagrelide is merely a predictable use of prior art elements according to their established functions. The claimed invention is not predictable because Applicant unexpectedly discovered that transdermally administering anagrelide to treat thrombocythemia as claimed minimizes the adverse cardiovascular side-effects observed when anagrelide is administered orally. These unpredictable results are discussed in the response filed September 19, 2007, the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Richard Franklin ("the Franklin Declaration") filed September 19, 2007, the response file March 28, 2008, and the response filed August 1, 2008.

These responses and Dr. Franklin's Declaration explain that Applicant determined the surprising cause of the adverse cardiovascular side-effects: 3-hydroxy anagrelide, formed during first-pass liver metabolism of orally administered anagrelide, inhibits phosphodiesterase III (PDEIII), an enzyme demonstrated to affect the cardiovascular system, 40 times more potently than anagrelide. These responses and Dr. Franklin's Declaration further provide 2 reasons for the non-obviousness of Applicant's invention. First, 3-hydroxy anagrelide inhibited PDEIII to a greater than expected degree in view of the relatively minor change to the structure of anagrelide. Second, the fact that the 3-hydroxy anagrelide metabolite causes undesirable side-effects represents the opposite of the expected metabolic detoxification process occurring in the liver.

Thus, the claimed invention of treating thrombocythemia by transdermally administering anagrelide thereby reducing the cardiovascular side effects observed when anagrelide is administered orally is not predictable and is non-obvious.

Thrombosis and thrombocythemia are distinct conditions.

The Declaration pursuant to 37 C.F.R. §1.132 by Gunnar Birgegård, M.D., Ph.D. ("the Birgegård Declaration"), filed herewith, explains that thrombosis and thrombocythemia are distinct conditions (*see* ¶¶4-6). Dr. Birgegård explains that thrombosis is a clot in a blood vessel caused by many different factors including, but not necessarily, myeloproliferative disorders such as essential thrombocythemia (ET) (*see* ¶5). In contrast, Dr. Birgegård discusses that thrombocythemia is an increased number of circulating platelets in the blood stream and may be part of a myeloproliferative disorder such as ET (*see* ¶6). Dr. Birgegård further explains that some conditions that cause thrombocythemia can increase the risk for thrombosis, however other conditions that cause thrombocythemia are not associated with thrombosis (*see* ¶6).

Dr. Birgegård also discusses the treatment methods for thrombosis and thrombocythemia (*see* ¶¶5-6). Notably, anagrelide is not a treatment for already existing thrombosis (*see* ¶5).

Specific comments responding to the Examiner's Remarks.

1. The Examiner notes that Applicant has presented evidence that thrombosis and thrombocythemia are distinct conditions treated by different pharmaceutical agents. However, the Examiner has chosen to give more weight to "the evidence that focuses on the similarities between the conditions and the overlap in treatments, including anagrelide." *See* page 3 of the Office Action.

Applicant asserts that despite any similarities that the Examiner may find between the two conditions, the presently claimed invention, based on the surprising finding that transdermally administered anagrelide minimizes the adverse cardiovascular side effects observed in patients who are orally administered anagrelide, would not have been predictable and, thus, not obvious as discussed above.

2. The Examiner discusses Miranda and D'Angelo on page 3 of the Office Action as follows:

> [a]pplicants also argue that the Miranda patent does not disclose anagrelide as a treatment of thrombosis but rather, only lists anagrelide once as one of over a dozen antithrombotic drugs and that D'Angelo does not describe or suggest the treatment or prevention of thrombocythemia. Admittedly, D'Angelo is a broad patent, and it does list numerous agents, including anagrelide, most importantly. However, the breadth of the patent does not in any way diminish its teachings. Stated another way, it is well understood in the art that the comprehensiveness of a disclosure does not negative its value for teaching each of the individual elements disclosed.

Applicant is assuming that, in the sentence "D'Angelo is a broad patent...," the D'Angelo reference should be replaced with the Miranda reference since Miranda, but not D'Angelo, discloses anagrelide. The Examiner continues by asserting that "the breadth of the patent does not in any way diminish its teachings."

Whether or not transdermally administered anagrelide can treat thrombosis is not the issue in determining whether the presently claimed invention is obvious. As discussed above, the obviousness of an invention rests on whether the claimed invention was predictable. The present invention was not predictable because one of ordinary skill in the art would not have expected a lack of cardiovascular side-effects in patients who are transdermally administered anagrelide compared to patients who are orally administered anagrelide.

Moreover, as pointed out above and by the previous responses, thrombocythemia and thrombosis are distinct conditions.

3. The Examiner asserts on page 3 of the Office Action that based on Dr. Franklin's Declaration, "[t]he effect appears still to be additive rather than synergistic." Applicant points out to the Examiner that the unexpected results discussed in the Franklin Declaration are not related to synergism.

4. The Examiner asserts a showing of *prima facie* obviousness in the paragraph bridging pages 3-4 of the Office Action. *Arguendo*, assuming the Examiner has presented valid *prima facie* obviousness rejections, Applicant has overcome the rejections by presenting evidence of the absence of an expected property. *See* MPEP 716.02(a)(IV) explaining that the absence of an expected property is evidence of nonobviousness and can be sufficient to overcome a *prima facie* obviousness showing. Each of the previous responses as well as the Franklin Declaration document and explain the unexpected absence of cardiovascular side-effects when anagrelide is administered transdermally.

For at least the reasons provided above, Applicant respectfully requests withdrawal of the obviousness rejections.

CONCLUSION

In view of the above remarks, it is respectfully requested that the application be reconsidered, that the response be entered, and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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